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Medical Progress

Acute Pancreatitis

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■ *For many decades two types of acute pancreatitis have been recognized: the edematous or interstitial and the hemorrhagic or necrotic. In most cases acute pancreatitis is associated with alcoholism or biliary tract disease. Elevated serum or urinary α-amylase is the most important finding in diagnosis. The presence of methemalbumin in serum and in peritoneal or pleural fluid supports the diagnosis of the hemorrhagic form of the disease in patients with a history and enzyme studies suggestive of pancreatitis.*

There is no characteristic clinical picture in acute pancreatitis, and its complications are legion. Pancreatic pseudocyst is probably the most common and pancreatic abscess is the most serious complication.

The pathogenetic principle is autodigestion, but the precise sequence of biochemical events is unclear, especially the mode of trypsinogen activation and the role of lysosomal hydrolases. A host of metabolic derangements have been identified in acute pancreatitis, involving lipid, glucose, calcium and magnesium metabolism and changes of the blood clotting mechanism, to name but a few.

Medical treatment includes intestinal decompression, analgesics, correction of hypovolemia and other supportive and protective measures. Surgical exploration is advisable in selected cases, when the diagnosis is in doubt, and is considered imperative in the presence of certain complications, especially pancreatic abscess.

"It is scant modesty for man, even if he is 'the highest vertebrate' to presume that he can predict the cosmic plan on the intensity of his joy and pain, or cement the stars together with even his highest aspirations."

HOMER SMITH. *From Fish to Philosopher;* Boston; Little, Brown, 1953.

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THE PANCREATIC ACINAR CELL segregates the enzyme protein from the cytoplasm immediately after its synthesis in order to avoid autodigestion. The endoplasmic reticulum, the Golgi complex, the zymogen granule membrane and the cell membrane proper constitute an effective interposition device covering the entire secretory cycle of the acinar cell. The pancreatic proteases (trypsin, chymotrypsin, elastase and carboxypeptidases) and phospholipase A are stored in the acinar cell and exist in the pancreatic secretion,

before it enters the duodenum, as inactive zymogen.[1,2] Trypsin plays the central role in the physiological activation of zymogen because the activation process consists of one or more trypsin catalyzed partial proteolysis reactions.[3] The stability of the entire zymogen system largely depends on the trypsin inhibitors which under normal conditions will prevent the trypsin activation of zymogen in pancreatic tissue and pancreatic secretion into the pancreatic ductal system.[4] Finally, healthy respiring acinar cells are not amenable to digestion by pancreatic proteases, because it has been shown that normal cell metabolism and cell membrane structure constitute important safeguards against enzyme-digestion.[5]

In acute pancreatitis inappropriate activation and release of enzymatic activity occurs in and around the pancreas[6,7] in pancreatic juice,[8] and into the blood stream.[9] The disease has been induced in various animals such as dogs, rats, cats, rabbits, goats and monkeys by a variety of methods, and certain forms of experimental pancreatitis bear some resemblance in microscopic pathologic features and in biochemical changes of the disease in man. Since the brilliant experiment of Claude Bernard in 1856,[10] two important questions remain unanswered, (1) how the various etiological factors initiate acute pancreatitis by overcoming the existing natural safeguards and (2) which mechanisms are responsible for the propagation of hydrolytic cleavage of cellular structures leading to generalized pancreatic necrosis and death.

Nonetheless, recent experimental and clinical data have provided some clues in the pathophysiology of acute pancreatitis and the time appears ripe to review previous information in the light of certain new developments. Since this review is mainly clinical, and recent reviews of etiological and pathogenetic mechanisms are available,[11,12] many important contributions will not be included. On the other hand, speculation and personal opinion on controversial points concerning pathophysiology, differential diagnosis, metabolic consequences and treatment will be discussed.

Etiology

Alcoholic Pancreatitis

The mechanism by which the heavy drinking of alcohol leads to acute attacks of pancreatitis remains unclear. Shapiro et al[13] have proposed a detailed hypothesis which includes stimulation of gastric acid secretion both by gastrin release in the antral mucosa and by direct stimulation of parietal cells. In turn, acid reaching the duodenum would promote secretion of secretin and pancreozymin with resultant stimulation of pancreatic secretion by all three gastrointestinal hormones. Concomitantly, a direct effect of ethanol on the sphincter of Oddi would increase sphincteric resistance[14-16] with resultant increase in intrapancreatic ductal pressure. Another proposed mechanism for alcoholic pancreatitis involves the reflux of bile into the pancreatic duct, but this suggestion remains at present purely hypothetical.[17] On the other hand, sphincteroplasty has been shown to reduce the incidence of pancreatitis even in patients who continue the intake of ethanol following this procedure,[18] a fact which probably indicates that reflux of bile does not play an important role in initiating alcoholic pancreatitis.

It has been shown that total obstruction of the pancreatic duct in dogs, combined with stimulation of pancreatic flow by endogenous or exogenous hormones, produces little pancreatic inflammatory response.[19] Recent studies suggest that a direct toxic effect of ethanol on the pancreas should be considered as at least partially involved in the production of pancreatitis. In the liver cells, structural changes have been described which probably represent a direct hepatotoxic effect of ethanol,[20-22] and it seems that a similarity exists between hepatic and pancreatic ultrastructural lesions, following the ingestion of ethanol in experimental animals. Darle et al[23] showed that in rats following long-term ethanol ingestion, the pancreas exhibited lipid droplets in acinar cells, swelling of mitochondria and reduction of their inner membranes, and cytoplasmic degradation of acinar and centroacinar and duct cells. Long-term ethanol ingestion is accompanied by decreased protein synthesis in the pancreas,[24] and by inhibition of uptake of ^{32}P into pancreatic phospholipids.[25] Furthermore, impairment of Na^+ dependent uptake of certain amino acids by pancreatic slices of alcohol-treated mice in vitro has been reported.[26] Further studies are required, however, to substantiate the direct toxic effect of ethanol on the pancreatic acinar cells and the mode of production of alcoholic pancreatitis.

Hyperlipidemia

Hyperlipidemia at times seen with acute pancreatitis may be (a) primary and a cause of pancreatitis, (b) secondary and a consequence of pancreatitis, and (c) a casual association with acute pancreatitis. Two of the primary hyperlipoproteinemias (type I and V) may be associated with bouts of abdominal pain due to pancreatitis.[27] Attacks of pancreatitis frequently begin in childhood and over the years lipemia retinalis, hepatosplenomegaly, and any of the many forms of xanthomas may be observed. Accurate classification of the lipid abnormality can usually be obtained with lipoprotein electrophoresis.[28]

Determination of lipoprotein lipase activity[29] is helpful in differentiating between type I and V. The cause of pancreatitis in familial hyperlipidemia is unknown. The episodes of acute pancreatitis are frequently mild and without severe complications.

Hypercalcemia

Hypercalcemia due to parathyroid adenoma,[30] parathyroid carcinoma[31] excessive doses of vitamin D,[32] multiple myeloma or calcium carbonate antacid overdose[33] might result in acute pancreatitis. The relationship between hypercalcemia and pancreatitis remains an uncertain one. Regardless of cause, hypercalcemia leads to an increase in calcium concentration and content in pancreatic juice. Data on experiments with dogs have shown that a rise in volume and bicarbonate concentration in pancreatic secretion is not accompanied by an increase in calcium concentration.[34,35] In patients with hyperparathyroidism there is increased calcium concentration in basal pancreatic secretion[36] and the same is true in experimental hypercalcemia in animals.[37] In chronic pancreatitis not related to hyperparathyroidism or hypercalcemia, there is high calcium content in basal pancreatic secretion.[36,38,39] It is noteworthy that the injection of soluble calcium compounds into the pancreatic ducts of rats results in severe acute pancreatitis.[40] In hyperparathyroidism acute pancreatitis has been attributed to conversion of trypsinogen into trypsin by high levels of calcium in pancreatic tissue and pancreatic secretion. Thus, in hypercalcemic rats increased levels of trypsin were found in pancreatic juice,[37] but no similar observation has been made in man. Pancreatic calcification is common in pancreatitis associated with alcoholism[41,42] hyperparathyroidism,[43,44] hereditary pancreatitis,[45,46] pancreatitis secondary to a duct obstructing pancreatic carcinoma,[43] rarely in pancreatitis accompanying biliary tract disease[41] and quite frequently in painless pancreatitis.

Solitary calculi obstructing the main pancreatic duct represent a variant of painless pancreatitis. The predominant form of calcium salt precipitation in the pancreas is calcium carbonate into the ducts, and less common is hydroxyapatite calcification deposited in areas of fat necrosis in the parenchyma.[47]

Biliary Tract Disease

The causative factors involved in the association of biliary tract disease and acute pancreatitis remain obscure. Recent work has focused on two areas of investigation: (a) the reflux into the pancreatic duct of altered components of bile such as unconjugated bile salts[48] and lysolecithin,[49] and (b) the identification of lymphatic channels as a pathway for the propagation of toxins with resultant pancreatic inflammation.[50] Deconjugation of conjugated bile salts could be effected by certain bacteria[48] and lysolecithin could be produced by the phospholipase A of pancreatic secretion acting upon bile lecithin.[49]

In one study unconjugated bile salts were detected in bile of patients with acute pancreatitis associated with gall bladder disease; and in another study,[51] of patients with acute cholecystitis, lysolecithin was identified in gall bladder as well as in hepatic bile. However, the most common known organism in bile, in biliary tree disease, is E. coli[52] which is unable to deconjugate bile salts. On the other hand, E. coli infected bile introduced under low pressure in the pancreatic ducts of cats had pronounced mucolytic and cytotoxic effects.[53]

Weiner and his associates[50] have shown that in dogs lymphatic communications do exist between the biliary tract and the pancreas. When acute cholecystitis was produced, by staphylococcal toxin injected into the gall bladder lymphatics or by lipase injected into the gall bladder, acute pancreatitis developed in a high proportion of animals. Furthermore, when india ink was infused into the lymphatics of the gall bladder, it entered the lymphatics in the interlobular spaces of the pancreas. Conversely, india

ink infused into the pancreatic lymphatics by ductal injection was demonstrated in lymphatics along the common bile duct.

Dixon and Hillam[54] pointed out that any speculation concerning the mechanism of acute pancreatitis associated with biliary tract disease should explain pancreatitis occuring with cholesterosis of the gall bladder, acalculous cholecystitis, acute and chronic calculous cholecystitis and choledocholithiasis with and without a "common channel." These investigations advanced the following three interesting possibilities: (a) a common underlying factor may be present in biliary tract disease and pancreatitis; (b) biliary tree disease may cause pancreatitis and (c) pancreatitis may cause biliary tree disease.

It is obvious from the preceding considerations that additional studies are required in order to identify the intricate mechanisms involved in this association, such as the role of bile salt deconjugating bacteria—for example, bacteroides, clostridia and streptococcus fecalis. It is possible that bacterial toxins from the biliary tree could find access to the pancreas through anastomotic lymphatic channels and could produce pancreatitis by labilizing cellular membranes with resultant release of pancreatic hydrolases, intracellular as well as exportable.

Hereditary Pancreatitis

Hereditary pancreatitis is a rare condition that manifests itself in childhood, in about half of the patients, and is inherited as a non-sex-linked Mendelian dominant, but poor penetrance of the gene and incomplete recessiveness have not been excluded. All patients have been white and most of them of northern European ancestry. In their patients with familial pancreatitis, Gross and his associates[55] found daily excretions as high as 1,600 mg of lysine and 848 mg of cystine and suggested that this specific aminoaciduria might represent a genetic defect or some other inborn metabolic error. However, aminoaciduria might be seen in some patients with non-familial pancreatitis and might be absent in half of the patients with the familial form. In the latter case the disease should be suspected when blood relatives have similar attacks of abdominal pain, in the absence of biliary tract disease or alcoholism and when there is a history of attacks beginning in childhood. In about half of the reported cases calcification of the pancreas has been found to occur in the larger pancreatic ducts[56,57] as gross calculi. Overt diabetes mellitus and exocrine insufficiency have been found in 20 to 25 percent of cases. The nature of the inherited predisposing abnormality remains unknown, and to date no other defect common to all affected persons has been recognized. Carcinoma of the pancreas has been reported to occur in some cases of hereditary pancreatitis.[58]

Postoperative Pancreatitis

Acute pancreatitis is a well recognized postoperative complication, mainly after biliary and gastric surgical operation although at times it occurs after operations in areas remote from the pancreas—for example, thyroidectomy or transurethral prostatectomy or orthopedic operations.[59] Contributing etiologic factors are trauma to the pancreatic tissue and ducts, and duct obstruction or compromise of blood supply producing ischemia with resultant autodigestion. In instances where local trauma cannot be responsible, hypovolemic shock,[60] the formation of microthrombi and a decrease of trypsin inhibitor in pancreatic juice have been cited as predisposing factors. The highest reported mortality in postoperative pancreatitis is 74 percent.[61] In a series of cases of pancreatitis following biliary tract operations, reported by Bardenheier and his associates,[62] common bile duct exploration and previous history of pancreatitis were considered the main contributory factors. The early postoperative diagnosis of pancreatitis is frequently difficult, and hypotension, oliguria, jaundice or a palpable mass in the upper abdomen, coupled with elevated serum and urinary amylase, should be helpful. With operative injury to the pancreas the amount of amylase in the urine increases, according to Ambromovage et al,[63] and the increment appears to be related more to the functional state of the gland than to the magnitude of pancreatic injury. Keighley and his associates[64] indicated that damage to the sphincter of Oddi in traumatic explorations of the common bile duct and sphincterotomy appear to be the most important factors for postoperative hyperamylasemia and pancreatitis.

Several recent reports of acute pancreatitis following extracorporeal circulation have appeared.[65-67] Johnson and Nabseth[68] reported a case of hemorrhagic pancreatitis following a cadaver renal transplant. Their survey of 1,321

renal transplants showed 23 cases of pancreatitis with 12 deaths. Speculated etiologic factors have been corticosteroid therapy, surgical trauma, induced auto-immune pancreatic rejection, decreased host protective responses and infection.

Pancreatitis in Pregnancy

The reason for the known tendency of acute pancreatitis of pregnancy to develop mostly during the last trimester or in the early postpartum period is obscure. Biochemical, hormonal and mechanical changes occurring during pregnancy and early puerperium might be important. To date, 106 cases of acute pancreatitis have been reported in association with pregnancy.[69] Biliary tract disease has been found in a substantial number of the cases.[70,71] Fatal hemorrhagic pancreatitis in pregnancy attributed to chlorothiazide administration has been reported,[73] and hyperparathyroidism in pregnancy has also been known to be a contributing factor. Maternal hyperparathyroidism leading to suppression of fetal parathyroid glands with resultant tetany in the child is known to occur.[73] Maternal mortality of 24.3 percent in 37 cases observed since 1951 was found by Berk et al.[69] Fetal mortality has also been high. Culdocentesis may be of special diagnostic value in pregnant women. The treatment is generally conservative, with termination of pregnancy to be considered when response to therapy is not satisfactory.

Drug-induced Pancreatitis

New cases of acute pancreatitis have been reported developing in the course of treatment with various therapeutic agents such as corticosteroids,[74,75] agents producing necrotizing angiitis in various organs including the pancreas,[76] salicylazosulfapyridine[77] and thiazides.[78] Acute pancreatitis in patients with acute leukemia and lymphoma during treatment with L-asparaginase (obtained from both A and B strains of E. coli), has been recorded.[79,80] L-asparaginase is known to arrest DNA synthesis and mitosis, in regenerating rat liver and abnormal liver function tests are common during L-asparaginase therapy in man. The mechanism of this kind of acute pancreatitis in man, however, has not been elucidated.

Generalized Infections

Acute pancreatitis has been associated with inflamatory processes through (a) lymphatic propagation from adjacent structures such as the gall bladder, (b) direct extension as in peritonitis, and (c) diseases in which another mechanism, possibly hematogenous spread, has to be considered. Examples of acute pancreatitis occurring in the course of severe bacterial infections have been recorded in typhoid fever, salmonella typhimurium infection,[81] scarlet fever,[82] streptococcal food poisoning,[83] and dysentery.[84] Furthermore, viral infections known to cause pancreatitis in man include viral hepatitis,[85] infectious mononucleosis[86] and mumps.[87] Acute pancreatitis has also been observed in animals infected with the encephalomyocarditis,[88] coxsackie group B[89] and foot and mouth disease viruses.[90]

Miscellaneous

Acute pancreatitis has been found to be associated with a multiplicity of other conditions such as systemic lupus erythematosus, electric shock,[91] methyl alcohol poisoning and atheromatous embolization to the intrapancreatic arteries,[92] to name but a few. In Trinidad, the most common cause of acute pancreatitis seems to be the sting of a scorpion.[93] Of particular interest is a recent series of 26 cases of pancreatic carcinoma associated with acute pancreatitis.[94] Obstructive lesions at the sphincter of Oddi cited recently as a cause of pancreatitis include benign polyps,[95] and regional enteritis of the duodenum.[96]

Despite the large number of known etiologic factors in acute pancreatitis, a group remains without a known cause—the idiopathic group. This group constitutes a variable proportion in the various reported series.

Diagnosis and Differential Diagnosis

Acute pancreatitis is a disease of variable intensity, and for many decades two types have been recognized: the edematous or interstitial and the hemorrhagic or necrotic. In most cases acute pancreatitis is associated with biliary tree disease or alcoholism. Acute alcoholic pancreatitis is usually seen in male patients 25 to 65 years of age who have been drinking heavily for five to ten years. There is no characteristic clinical picture in acute pancreatitis and the manifestations may vary from a bout of vague dyspepsia, with slight abdominal pain, to a fulminating collapse with shock and death. More often than not, the outstanding symptom will be

steady, severe epigastric pain, frequently radiating to the back. The most important laboratory test is an elevated serum and urinary α-amylase. In acute pancreatitis, the serum amylase is elevated within two to twelve hours of onset. If there is no rise within 24 hours, the diagnosis probably is not acute pancreatitis. The timed two-hour urinary amylase appears to be a better test because it remains elevated after the serum amylase has returned to normal, usually within two to three days. Recently, an entirely new approach to the assay of amylase has been developed using an insoluble starch labeled covalently with Remazolbrilliant blue and other dyes.[97-100] Two of the methods utilizing the new starch substrates have been automated.[101,102] These new assays have been shown to be simple and rapid and the results highly reproducible. They are considered much superior to the saccharogenic or turbidimetric methods. Whereas it is known that no relation exists between the severity of pancreatic inflammation and the degree of serum amylase elevation, the fact that serum amylase might not be elevated at the time of admission is perpetually ignored, and the assays of urinary amylase are neglected. Such omissions lead to faulty evaluations of the value of amylase determinations in the differential diagnosis of acute pancreatitis.[103] Recent studies have shown that the renal clearance of amylase increases in acute pancreatitis.[104-106] If acute pancreatitis is suspected and serum amylase has returned to normal, determination of the ratio of amylase clearance to simultaneously assayed creatinine clearance might have some value in supporting the diagnosis of pancreatitis. However, an increased serum lipase and two-hour urinary amylase level offer a reasonably accurate diagnosis.[107] Measurements of serum lipase activity have not been widely used because of the long incubation times involved, the instability of the substrates and the technical difficulties of the available methods. A suitable lipase assay must be rapid and must utilize a substrate that is stable, specific for lipase of pancreatic origin and is hydrolyzed to yield a product that can be easily measured. In a recently introduced rapid, automated specific assay method for lipase, monodecanoyl fluorescein is used as substrate.[108] Serum levels of lecithinase A and deoxyribonuclease activity have been found to be elevated in acute pancreatitis but determination of these factors has not gained wide use. Since trypsin and chymotrypsin are exclusively found in the pancreas, the assay of increased trypsin and chymotrypsin in serum should be specific for the distinction of acute pancreatitis from other diseases. However, chemical methods introduced for the assay of trypsin or chymotrypsin in serum are unsuitable for this purpose because of the lack of substrate specificity, lack of sensitivity and the presence of protease inhibitors.

A radioimmunoassay technique has now been developed for the determination of α-chymotrypsin in bovine and human serum,[9] which seems to obviate the difficulties which are inherent to the chemical methods. With this technique a threefold increase in serum chymotrypsin levels was found in patients with acute pancreatitis as compared with normal individuals. Further work is needed, however, for complete evaluation of the usefulness of this immunoassay method in the diagnosis of pancreatitis.

The differential diagnosis of acute edematous or interstitial, from hemorrhagic pancreatitis is significant in prognosis and therapy. The early detection of methemalbumin (0-24 hours) in serum of patients with hemorrhagic pancreatitis, in the presence of haptoglobin, has been suggested for this purpose. This test has been unduly discredited by recent reports.[109,110] Whereas, pancreatic enzymes, mainly trypsin, lipase and elastase can convert hemoglobin into hematin *in vitro*,[111] it seems that tissue enzymes might be also effective *in vivo*. It has been shown that methemalbumin may occur in the serum in several other conditions such as ruptured ectopic pregnancy, severe postoperative intraperitoneal hemorrhage, superior mesenteric artery thrombosis, intrahepatic hematoma, strangulation obstruction and intravascular hemolysis. However, when methemalbumin is detected within the first 24 hours in the serum or in pleural or ascites fluids in a patient with a history and enzyme studies compatible with acute pancreatitis, the diagnosis of the necrotizing form is justified.[112] Plain films of the abdomen have diagnostic value when the "sentinel loop" is present and they also contribute to the differential diagnosis of perforated peptic ulcer or other acute conditions. Additional studies are needed for the evaluation of newer techniques such as the celiac angiogram and the echogram.

Certain Clinical Features and Complications

Pain has always been considered as the main symptom in acute pancreatitis and it is usually epigastric and less often generalized over the whole abdomen. The classic "bandlike" abdominal pain is encountered in a relatively few patients. Only recently, clinicians have realized that at times acute necrotizing pancreatitis may present itself without appreciable pain. Tachycardia, sweating, nausea and vomiting are almost always present. In the course of both interstitial and hemorrhagic pancreatitis large amounts of protein-enzyme rich fluid escape around the pancreas and, in addition to hypovolemia, may cause destruction of nearby tissues.

The complicating features in acute pancreatitis are legion. Stenosing lesions of the colon[113] and colonic fistulization[114] may occur. Mesenteric fat necrosis, producing thrombosis of mesenteric vessels may result in jejunal infarction.[115,116] The urologist should include acute pancreatitis in the differential diagnosis of upper urinary tract lesions, such as changes in the left kidney producing painless hematuria.[117] Rupture of the esophagus[118] and spleen[119] and massive intraperitoneal bleeding due to erosion of the left gastric artery[120] have been reported. Pleuropulmonary complications include basilar atelectasis, pleural effusion, pneumonitis, pulmonary embolus and infarction, empyema and respiratory difficulties due to a pseudocyst formation in the mediastinum.[121,122] A grave complication of pancreatic pseudocysts is bleeding into the cyst[122,124] with subsequent rupture into the stomach, bowel or biliary tree, producing hemobilia and massive upper gastrointestinal hemorrhage.[125] Pseudocysts are relatively rare in childhood and most of the 55 reported cases are due to trauma[126,127] or pancreatitis (mumps). Pseudocysts of the pancreas are so designated because they do not contain an epithelial lining and therefore are not true cysts. The clinical features of pancreatic pseudocysts are highly variable and frequently misinterpreted. Pseudocysts may bleed,[128] erode into adjacent structures,[117,125,129,130] or rupture into the peritoneal cavity, the mediastinum[131] or into the portal vein,[132] or they may cause obstructive jaundice or mimic neoplasm. Individualization of management is required, and is based on location and maturity of the cyst's wall for a safe internal drainage.[133,134]

Perhaps the most serious and least appreciated complications of acute pancreatitis are pancreatic abscesses and lesser omentum collections. They occur in the course or following an attack of pancreatitis, and the causative organism is usually one or more Gram-negative bacteria.[135] In a recently reported series bacterial growth was obtained in 60 of 74 cases.[136] E. coli was seen in 16, Aerobacter aerogenes in nine and Staphylococcus aureus in eight; and more than one organism was present in 30 percent of the cases. External drainage is considered to be the standard procedure in pancreatic abscess, and without surgical intervention the outcome is usually fatal with generalized sepsis.[135,137]

A number of patients with acute pancreatitis have been observed who have become acutely confused during the course of the attack. The patients become very restless, disoriented and difficult to control. The "pancreatic encephalopathy" is most probably caused by the toxic effect of circulating enzymes on the brain[138] and the pathological picture is that of widespread demyelinization and diffuse small hemorrhages in the brain. Central pontine myelinolysis associated with acute pancreatitis has also been reported.[139] Shock complicating acute pancreatitis is an ominous prognostic sign.[140] Its mechanism is at least in part a critical reduction of plasma volume, and oliguria, hyperamylasemia and metabolic acidosis are some of the features. Recent information suggests that the shock of acute pancreatitis should not be considered strictly toxic or strictly hypovolemic. French workers have introduced the term "enzymatic toxemia." Prompt plasma volume replacement favors reversal of the hemodynamic and metabolic deficits in some cases.

Nitrogen retention in acute pancreatitis indicates poor prognosis and the precise mechanism by which pancreatitis impairs renal function is unknown. It is possible that complex vascular and humoral factors are involved.

Pathogenetic Mechanisms Initiating and Propagating Pancreatic Inflammation

Despite the accumulation of a vast amount of experimental data, attemps to relate the several etiologic factors to a single pathogenetic mechanism in acute pancreatic inflammation have

failed. A complete review of existing information is beyond the scope of this communication, and only pertinent recent information will be discussed. The pancreas in the average man, weighs about 70 grams (0.1 percent of body weight) and has 13 times the protein-producing capacity of the liver and reticuloendothelial system combined[141] (4 percent of the body weight). Cannulated steer pancreas produces about 1 gram of protein per hour, and 20 percent of the dry weight of the organ constitutes enzyme-protein. With the exception of the mucosa of the gastrointestinal tract, the pancreas is the most rapidly autolyzed body tissue after death.

Normally, the pancreatic proteases and phospholipase A are stored in the exocrine cell as inactive percursors. The ergastoplasm, the Golgi complex, the zymogen granule and the cell membrane proper segregate the exportable pancreatic enzymes in the acinar cell. The same is true for the lysosomal hydrolases which co-exist with the exportable enzymes in the same cell. As an additional safety device against intracellular activation of trypsinogen (the crucial step in the mechanism of zymogen activation) two protease inhibitors are present in the exocrine cell. The interrelationship between lysosomal and exportable enzymes in the biochemical events of acute pancreatitis is not clear. A protease, probably of lysosomal origin, was recently identified in pancreatic secretion with pH optimum between 3 and 5, which is capable of activating trypsinogen into trypsin.[142] Whether such a low pH can be attained in the microenvironment of the exocrine cell is a matter of speculation. The possibility of spontaneous activation of trypsinogen under certain metabolic conditions (hyperparathyroidism, for example) is also possible but requires further documentation.

Proteolytic enzymes have been recovered from pancreatic tissue during the course of experimental pancreatitis,[143] and have been identified in ascites and pleural fluid in acute pancreatitis in man;[7,144] phospholipase A is present in the exudate of experimental pancreatitis[145] in dogs, and chymotrypsin has been detected in the serum of patients with acute pancreatitis.[9] The available evidence strongly suggests that the pathogenetic principle in acute pancreatitis is autodigestion, but the intricate sequence of events remains to be established. Elastase and phospholipase A appear to be significant for coagulation necrosis, vascular injury and hemorrhage. In human pancreatic tissue undergoing necrosis, lysolecithin increased and lecithin decreased, presumably as a result of phospholipase A action.[146] Elastase which has been shown to exist in zymogen form in the acinar cell,[147] appears to play an important role in the destruction of elastic tissue of intrapancreatic vessel walls in hemorrhagic canine[148,149] and human pancreatitis.[150] Recent evidence indicates that under certain conditions a potentiating effect might exist between trypsin and chymotrypsin on elastase as related to elastolysis.[151] Trypsin appears significant in its catalytic action, by activating inactive zymogen, with resultant hydrolytic cleavage of cellular structures, elastolysis and activation of the bradykinin system. Vasoactive polypeptides may account for the glassy edema,[152] and the unduly severe pain in acute pancreatitis. Pancreatic exudate was shown to contain strong kininogenase activity,[152] and could cause hypotension when given intravenously.[153]

Vascular factors in the pathogenesis of acute pancreatitis have received new emphasis in recent reports. In experimental pancreatitis red blood cells have been shown to obstruct lymphatics communicating with pancreatic interstitial spaces,[154] with resultant intensification of the inflammatory reaction. In acute hemorrhagic pancreatitis significant reduction of both pancreatic blood flow and perfusion was found,[155] which would further enhance local ischemia.

Whereas it appears impossible at present to incriminate a single pancreatic enzyme in the pathogenesis of acute pancreatitis in man, the combined action of proteolytic and lipolytic enzymes and of vasoactive polypeptides could explain the histopathologic features and the biochemical consequences of the disease. A plausible, hypothetical, common denominator of the pathogenetic mechanism could be an increase in permeability of cellular lipoprotein membranes surrounding the exportable and lysosimal hydrolases in the acinar cell by variety of factors capable of disturbing cell metabolism and cell membrane structure. Such factors could include endotoxins, exotoxins, viral infections, low pH (acidosis), ischemia-anoxia and direct injury to the pancreas, with resultant initiation of the autocatalytic mechanism.

Metabolic Abnormalities in Acute Pancreatitis

Lipids

The appearance of lactescent serum during an attack of acute pancreatitis is well recognized and is thought to occur in from three to eight percent of cases.[156] It is noteworthy that in pancreatitis with hyperlipemia, serum amylase and lipase values may be normal and it is assumed that gross hyperlipemia interferes with the assay of these enzymes. Thus, urinary amylase determinations are of great value in the diagnosis of pancreatitis in the presence of serum lactescence. It appears that hypocalcemia or tetany or both may complicate acute pancreatitis more frequently when it is associated with hyperlipemia. In a recent series,[157] seven of nineteen patients had hypocalcemia. The syndrome of hyperlipemia that follows pancreatitis is seen most commonly in alcoholics with a type IV lipoprotein electrophoretic pattern, but types I and V have also been reported.

Zieve[158] presented evidence in support of the thesis that hyperlipemia seen in acute pancreatitis results from the liver injury due to alcoholism and malnutrition. A number of other mechanisms have been proposed to explain the hyperlipemia due to acute pancreatitis, among them subclinical defects of lipid metabolism associated with decreased ability to clear circulating triglycerides,[156] transient decrease or inhibition of lipoprotein lipase activity,[159,160] and decreased availability of insulin with resultant defective clearing of dietary lipidemia.[161] However, data concerning plasma insulin levels in acute pancreatitis are scanty,[162] and it would be interesting to know the insulin activity in patients with and without hyperlipemia in the acute phase of the disease. Decreased insulin reserves apparently exist in chonic pancreatitis.[163-165] The difficulties in explaining the hyperlipemia of acute pancreatitis are compounded by the fact that the ingestion of large amounts of alcohol alone can result in moderate triglyceridemia. Ethanol enhances triglyceride synthesis by the liver[166] and the intestine,[167] might decrease lipoprotein lipase activity,[168] and might increase growth hormone and 11-hydroxycorticoid levels[169] in plasma. High levels of plasma cortisol were also found in ten patients with acute pancreatitis and hyperlipidemia.[170] It is known that, in the presence of glucocorticoids, low concentrations of growth hormone stimulate lipolysis, an effect which is said to be mediated by 3′, 5′—cyclic adenosine monophosphate and is blocked by insulin. It is also known that growth hormone and glucocorticoids are involved in the mobilization of fat in animals deprived of food or insulin. Additional work is needed, however, aimed at the clarification of the role of hormonal factors in the pathogenesis of hyperlipidemia associated with acute pancreatitis and alcoholism.

Calcium

Hypocalcemia in the course of acute pancreatitis has been attributed to calcium soap formation in areas of fat necrosis. This theory does not take into account the vast calcium stores in bone, which are rapidly and readily available and can be mobilized within a few hours. Thus, Holland et al[171] showed that serum calcium levels returned to normal in one hour after severe hypocalcemia was induced by infusion of sodium ethylenediamine tetraacetic acid. Large doses of parenterally administered calcium, in patients with acute pancreatitis, often do not raise serum calcium to the expected level. Two additional mechanisms have recently been proposed in order to explain the hypocalcemia of pancreatitis. Increased levels of serum glucagon known to occur during attacks of acute pancreatitis[172] might produce hypocalcemia by stimulating the secretion of thyrocalcitonin with resultant inhibition of bone resorption.[173] It has been shown that glucagon hypocalcemia can be induced in dogs with an intact thyroid but not after thyroidectomy, and *in situ* perfusion of the thyroid with glucagon resulted in a rapid fall of calcium levels.[173] However, despite this suggestive experimental evidence in dogs, glucagon infusion failed to increase serum calcitonin levels in the majority of the normal humans tested.[174] On the other hand, Stern and Bell[175] demonstrated that in tissue culture, using embryonic rat bone labeled with ^{45}Ca, glucagon directly inhibits bone resorption, induced with either parathyroid hormone or dibutyryl-3′-5′-adenosine monophosphate, indicating an additional glucagon action independent of thyrocalcitonin.

Another possible mechanism for the production of hypocalcemia is the concomitant hypomagnesemia,[176] which would make bone refractory to parahormone action.[171] The incidence of hy-

pomagnesemia in acute pancreatitis should be further investigated, especially in cases of the alcoholic variety, the better to assess its role in hypocalcemia. Furthermore, serum glucagon, parahormone and thyrocalcitonin should be determined in a large number of cases of acute pancreatitis, in order to substantiate the significance of hormonal factors in this type of hypocalcemia.

Endocrine Function

During an episode of acute pancreatitis, hyperglycemia and glycosuria develop in a large proportion of patients, and some of them have permanent diabetes following the attack.[178] Whereas injury to the b-cells due to the pancreatic inflammation appears to be the most plausible explanation for this phenomenon, other events such as release of glucagon[179-181] and glucocorticoids[182] might also contribute to the hyperglycemia in acute pancreatitis.

In chronic pancreatitis, the concomitant decrease of a-cell and b-cell function manifests itself by "brittle" pancreatic diabetes. This could also explain the prolonged hypoglycemic response noted in patients with chronic calcific pancreatitis[183] following the intravenous administration of insulin. The effect of glucagon on pancreatic function has been studied in recent years. Administration of glucagon to dogs with pancreatic fistulae depresses the rate of flow, volume and enzyme concentration of pancreatic juice secreted by the pancreozymin/secretin-stimulated gland.[184,185] Similar observations in humans have suggested a possible regulatory role for glucagon in the control of exocrine pancreatic secretion.[186] The possibility has been raised of a compensatory hypersecretion of glucagon in acute pancreatitis, with resultant suppression of pancreatic and gastric secretions and inhibition of gastrointestinal motility. On the basis of these observations, it has been suggested that glucagon might have therapeutic value during an attack of pancreatitis.[187]

Blood Coagulation

Various coagulation abnormalities associated with acute pancreatitis have been described, but diffuse hemorrhage or widespread thrombosis occurs rarely.[188] The most frequent abnormalities are prolongation of the whole clotting time and prothrombin time and a decrease of fibrinogen and factors II, VII and IX with an elevation of the antithrombin titer. The precise mechanism for these abnormalities has not been established. However, the release of pancreatic proteases (for example, trypsin, chymotrypsin and elastase) into the circulation constitutes a plausible explanation of the changes in the clotting mechanism. For instance, trypsin can activate factor X *in vitro*,[189] convert prothrombin into thrombin[190] and digest fibrinogen and other clotting factors. Furthermore, improvement of coagulation variables and correction of hypofibrinogenemia have been demonstrated following the administration of a protease inhibitor from beef lung (Trasylol®)* and epsilon aminocaproic acid.[191] A response to these agents probably indicates an important role for proteolytic enzymes in bringing about coagulation abnormalities in acute pancreatitis. Greipp and his associates[192] observed a patient with acute pancreatitis, complicating the administration of L-asparaginase, and found very low plasma fibrinogen and abundant fibrinogen degradation products in the blood. In a recent experimental study, small doses of trypsin were injected intravenously into rabbits, with resultant rapid decrease of fibrinogen and of platelets.[193] Electronmicroscopic examination of the renal glomeruli showed thrombi containing numerous platelets and fibrin, and light microscopy revealed microthrombi in several organs. Similar phenomena have been observed in experimental[194] and clinical hemorrhagic pancreatitis.

Further studies *in vitro* and *in vivo* are required for a better understanding of the role of various hydrolases, such as trypsin, chymotrypsin, elastase, the phospholipases and the lysosomal enzymes, in the production of coagulation abnormalities in acute pancreatitis.

Treatment

Medical Management

The treatment in acute pancreatitis includes the use of nasogastric suction, analgesics, and the intravenous infusion of colloids and crystalloids, using central venous pressure, hourly urinary output, blood pressure and hematocrit as guides. Colloid loss is replaced with human albumin and with plasma or whole blood. Seriously ill patients will require two to six units of albumin or

*Not available on the commercial drug market in the United States.

plasma or whole blood the first 24 hours in order to maintain good peripheral perfusion.[195-197] In cases of hypocalcemia with tetany, intravenous infusion of calcium will alleviate tetany without necessarily restoring serum calcium levels to normal. In the presence of significant hyperglycemia or in cases of acute pancreatitis presenting as hyperosmolar coma, insulin therapy is indicated. Morphine and meperidine (pethidine) are perhaps the two drugs most commonly used for pain of biliary or pancreatic origin, but both produce a decided rise in biliary pressure. Recent evidence suggests that pantazocine is the most appropriate strong analgesic in biliary and pancreatic disease.[198] Anticholinergic preparations have been used in acute pancreatitis in order to suppress gastric and pancreatic secretion, but their effect remains unclear.[199] Their effectiveness in reducing biliary and pancreatic duct pressure is unknown. However, butylscopolamine has been found to produce a pronounced and sustained depressing effect on the morphine-induced pressure elevation in the common bile duct.[200] The usefulness of Trasylol, the protease inhibitor obtained from beef lung, remains unproved and this type of antienzyme therapy has not gained acceptance in this country.[201-203] Intra-arterial infusion directly into the celiac artery did not improve the results in a recent series.[204] Trasylol does not inhibit the elastolytic activity of pancreatic elastase, and has no effect on lipase and phospholipase A. Furthermore, *in vitro* studies have shown that the concentration of this inhibitor sufficient to reduce the activity of a mixture of chymotrypsin and trypsin to a residual baseline reading is not capable of eliminating the potentiating effect of these enzymes on elastase activity. Recent studies with purified human trypsin have shown that this enzyme is not inhibited by soybean trypsin inhibitor and ovomucoid,[205] a fact attributed to possible differences in tertiary structure of the human enzyme as compared with other trypsins. Detailed *in vitro* inhibition studies of all human pancreatic proteases, with naturally occurring and synthetic inhibitors are required. A recent report indicates a beneficial effect in the treatment of acute pancreatitis with a new elastase inhibitor.[206] In cases of acute hemorrhagic pancreatitis the use of peritoneal lavage[207] has been advocated as well as general supportive measures.[208] For a definitive evaluation of peritoneal lavage in hemorrhagic pancreatitis[209] without or with drainage of the thoracic duct,[210] a controlled randomized study in a sizable number of patients is highly desirable. Experimental studies in dogs have shown that agents such as low molecular weight dextran,[211] fibrinolysin or heparin[212] offer considerable protection against the development of hemorrhagic pancreatitis induced by the intraductal injection of trypsin-digested blood. The same was true for animals subjected to postganglionic sympathectomy.[213]

The prophylactic use of antibiotics for the prevention of secondary infection in severe cases of acute pancreatitis is purely empirical at this point and no controlled studies exist in the literature concerning the effectiveness of these agents. However, the theoretical basis for their use is as follows: In acute pancreatic inflamation there is pancreatic and peripancreatic edema due to the exudation of protein-enzyme rich fluid. The peripancreatic edema may spread to the retroperineal space, the mediastinum, the mesentery and other areas. The protein rich exudate, in edematous poorly perfused tissues, is favorable to bacterial growth. Antibiotics are given with the object of providing an effective concentration in this fluid. Superimposed infection constitutes the most lethal late complication in acute pancreatitis and it is difficult to localize. Most pancreatic abscesses contain one or more Gram-negative bacillus and other bacteria. In choosing an antibiotic in acute pancreatitis, one must remember that hepatotoxicity and renal toxicity should be avoided. Every attempt should be made, of course, for identification of the causative microorganism(s) by blood and peritoneal fluid cultures followed by sensitivity tests. We have mainly used ampicillin, but chloramphenicol, gentamycin or cephalothin with or without kanamycin have been used at times, on the basis of positive blood cultures and sensitivity tests, under constant monitoring of urinary output. Whether bowel sterilization techniques could be beneficial in acute pancreatitis, as prophylaxis against infection, is unknown.

Surgical Management

Accurate diagnosis in a patient with severe abdominal pain, tachycardia and shock, especially when seen late in the course of the disease, may be difficult indeed. Earlier reports suggested a high mortality associated with laparotomy in

patients with acute pancreatitis. However, many of the deaths occurred in the terminal stage of serious illness. Recent studies indicate a low mortality with early laparotomy.[214,215] Thus, when acute pancreatitis is suspected the patient is treated vigorously for four to six hours and if the diagnosis is in doubt and the patient is deteriorating despite vigorous supportive therapy, exploratory laparotomy is indicated. The literature does not provide a clear answer to the problem of acute pancreatitis associated with biliary tree disease. Patients with gangrene or perforation of the gall bladder or acute suppurative cholangitis require operation whether or not they have hyperamylasemia or pancreatitis.[54] For patients with severe pancreatitis who respond to treatment slowly, definitive biliary tract operation should be delayed from four to six weeks after complete recovery from acute pancreatitis.[216] An upper abdominal mass suspected of being a pseudocyst, especially one that expands suddenly and gives evidence of intra-abdominal leakage, needs surgical intervention. Persistent rising jaundice necessitates surgical decompression of the biliary tree. If at laparotomy, acute hemorrhagic pancreatitis is found, adequate aspiration of the peritoneal cavity should be carried out and large sump drains should be placed around the pancreas.[217] Total pancreatectomy early in necrotizing pancreatitis, as advocated by some investigators, seems overly drastic in view of the extensive local reaction present.[218,219] Should a pancreatic abscess develop, with spiking fever, high leukocyte counts and evidence of intraabdominal sepsis, surgical drainage is imperative. The nonalcoholic patient presenting with severe pancreatitis and no evidece of acute cholecystitis constitutes a difficult problem. Choledocholithiasis, at the lower end of the common bile duct, is the commonest biliary lesion found in such cases. The treatment is initially conservative, with the patient observed for signs of resolution of the acute attack, and an operation is undertaken later for removal of the stones.

The mortality rate for acute hemorrhagic pancreatitis remains high, especially when renal impairment and azotemia are present. Edematous pancreatitis has a low mortality, except when delirium tremens is present concomitantly. In hemorrhagic pancreatitis the extent of necrosis, and in both the hemorrhagic and edematous forms coexisting disorders such as fatty liver, myocardiopathy and renal disease, constitute important factors affecting the prognosis in the individual patient.

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POST-INTUBATION TRACHEAL STENOSIS

Once patients with post-intubation tracheal stenosis begin to develop symptoms, they are awfully close to obstruction. We have found in patients who are still sedentary from the disease that originally required their respiratory therapy that their airway gets down to about 5 mm before they begin to have symptoms. One of the people in our medical pulmonary unit has done some experiments with volunteers and also measured patients and found that until the airway gets down to the critical diameter of 5 to 6 mm patients at rest really don't have symptoms. This is sort of startling but it is a fact. Most of the patients we have seen have had about the same cutoff point when their condition became obvious or they became totally obstructed.

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